# Hydroxyethyl-starch use and PBM: a necessary update to the italian national guidelines

Gianni Biancofiore[1], Stefania Vaglio[2], Giancarlo M. Liumbruno[2]

*[1]Anaesthesia and Critical Care for General and Transplantation Surgery, University Hospital, Pisa; [2]Italian National Blood Centre, National Institute of Health, Rome, Italy*

Dear Sir,

Fluid therapy has always been considered as a cornerstone of surgical and critically ill patients. However, uncertainty about the appropriate choice of fluid for volume replacement persists.

Crystalloids and colloids, the two major categories of fluid therapy used, have been the subject of an ongoing debate as to which of the two is the safer and more effective resuscitative fluid.

Colloids have been used as volume expanders for acute fluid resuscitation in shocked patients. This is because colloids are thought to have longer intravascular persistence and therefore a longer volume replacement effect resulting in lower total volume needed and less extravascular oedema. However, synthetic colloids may negatively affect coagulation and are potentially nephrotoxic. "Modern" hydroxyethyl starches (HES) were considered relatively safe and were widely used, especially in Europe, until recently. However, HES solutions have been recently shown to increase both mortality and the risk for renal replacement therapy among some classes of critically ill patients. Accordingly, their indications have been significantly restricted.

On 14 June 2013, following a review of the available evidence, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefits of infusion solutions containing hydroxyethyl-starch (HES) no longer outweigh their risks and therefore recommended that the marketing authorisations for these medicines be suspended[1]. Consequently, the Italian National Drug Agency introduced a measure for the withdrawal of all remaining stocks of HES solutions at clinicians' disposal[2]. Accordingly, in its recommendations for the application of a Patient Blood Management (PBM) programme in elective major orthopaedic surgery in adults, the experts from the Italian National Blood Centre outlined that HES solutions should not be used to correct acute hypovolaemia in bleeding patients because of the increased risk of mortality and renal failure[3]. However, in a following document[4], the PRAC modified its recommendation. In fact, the Committee confirmed that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality but concluded that HES solutions may continue to be used in patients to treat hypovolaemia caused by sudden blood loss where treatment with alternative infusions solutions (namely "crystalloids") alone are not considered to be sufficient. Moreover, in order to minimise potential risks in these patients, the PRAC recommended that HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration. Consequently, the Italian National Drug Agency made HES solutions available for clinical use exclusively in hypovolaemic, haemorrhagic patients[5].

Therefore, the Authors of the Italian national guidelines on PBM wish to hereby acknowledge what the PRAC and the Italian National Drug Agency outlined in their latest statements that partially modifies the recommendation included in the previously published guidelines where they refer to HES solutions[3]. Accordingly, the following recommendation: "it is recommended that hydroxyethyl starch solutions are not used to correct acute hypovolaemia in bleeding patients because of the increased risk of mortality and renal failure [1B]" is now to be considered modified as follows: "hydroxyethyl starch solutions may be used in patients with hypovolaemia caused by sudden blood loss where treatment with crystalloids alone are not considered to be sufficient" [1B].

Hopefully, in the next years new data about the safety and efficacy of HES solutions will be provided by currently ongoing studies possibly putting an end to a, so far, never ending controversy.

*The Authors declare no conflicts of interest.*

## References

1) European Medicines Agency. PRAC recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl-starch. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Solutions_for_infusion_containing_hydroxyethyl_starch/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144448.pdf. Accessed on 04/04/2016.

*Blood Transfus* DOI 10.2450/2016.0061-16

2) Agenzia Italiana del Farmaco. Comunicazione sul divieto di utilizzo cautelativo per i medicinali per uso infusionale contenenti amido idrossietilico. Available at: http://www.agenziafarmaco.gov.it/it/content/comunicazione-sul-divieto-di-utilizzo-cautelativo-i-medicinali-uso-infusionale-contenenti-am. Accessed on 24/02/2016. [In Italian.]
3) Vaglio S, Prisco D, Biancofiore G, et al. Recommendations for the implementation of a Patient Blood Management programme. Application to elective major orthopaedic surgery in adults. Blood Transfus 2016; **14**: 23-65.
4) European Medicines Agency. PRAC confirms that hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients. Available at:http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001917.jsp&mid=WC0b01ac058004d5c1. Accessed on 24/02/2016.
5) Agenzia Italiana del Farmaco. Nota Informativa Importante sulla restrizione d'uso di HES (medicinali contenenti amido idrossietilico). Available at: http://www.agenziafarmaco.gov.it/it/content/nota-informativa-importante-sulla-restrizione-d%E2%80%99uso-di-hes-medicinali-contenenti-amido-idros. Accessed on 24/02/2016. [In Italian.]

Arrived: 12 March 2016 - Revision accepted: 14 March 2016
**Correspondence:** Gianni Biancofiore
UTI Trapianti
Azienda Ospedaliera Universitaria Pisana
Via Roma, 67
56126 Pisa, Italy
e-mail: g.biancofiore@med.unipi.it